UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/595,682	06/16/2000	Mary K. Danks	SJ-0005	1625

31949 7590 09/24/2003

LICATA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/595,682	DANKS ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,18 and 22-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14,18 and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 12-14, 18 and 22-29 are pending in the application.

This Office Action is in response to the Amendment filed on 7/9/03.

Response to Amendment

Claims 12-14, 18 and newly added claims 22-29 stand rejected under 35 U.S.C.112 1st paragraph for reasons set forth of the record mailed on 4/9/03 and further discussed below.

Newly added claims 22-24 are rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14, 18 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for sensitizing tumor cells to chemotherapeutic prodrug APC or CPT-11 *in vitro*, comprising transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter directs specific expression of said carboxylesterase in said tumor cells, wherein expression of said carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic drug; a method of inhibiting tumor cell growth *in vitro*, comprising sensitizing tumor cells by transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter

directs specific expression of said carboxylesterase in said tumor cells, contacting said tumor cells with chemotherapeutic prodrug APC or CPT-11 so that the tumor growth is inhibited; said methods while applied *in vivo*, wherein the polynucleotide encoding the rabbit carboxylesterase is carried by an adenoviral vector which is administered intratumorally or intravenously, and the chemotherapeutic drug is administered intravenously, does not reasonably provide enablement for such method for *in vivo* application, wherein the polynucleotide encodes any carboxylesterase, and the said enzyme and chemotherapeutic drug are delivered by any route. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In response to the rejection, Applicants argue that the claimed method is enabled to its full scope because multiple delivery systems are taught in the specification. Further, Applicants provide a Declaration and a package insert of a prodrug Xeloda to prove that multiple means of delivery of the prodrug and nucleic acid encoding the carboxylesterase is enabled.

These arguments have been fully considered but deemed not persuasive. The technical difficulties and unpredictable nature of gene therapy is discussed in detail in the previous office actions. The teaching of the specification cited by Applicants (page 7, 15 and 28) does not overcome such difficulties and unpredictability for successful gene therapy. The information discussed in the package insert of Xeloda does not overcome such unpredictability either. Xeloda is a prodrug of chemotherapeutic agent 5-FU which relies the catalytic activity of a number of liver enzymes for its conversion to active drug. However, the claimed method involves administering a nucleic acid encoding a carboxylesterase to tumor cells with a chemotherapeutic prodrug, which is entirely different from administering a prodrug by itself.

Thus, successful oral administration of Xeloda does not provide support for the claimed method by this route of administration. The Declaration demonstrates expression of human intestinal carboxylesterase (hiCE) by two Herpes simplex viral vectors in a human glioma cell line. However, the Declaration fails to provide further evidence that such *in vitro* expression would translate into expression at sustained and high enough level *in vivo* to sensitize tumor cells to chemotherapeutic drug. Most importantly, it does not support the successful delivery by any routes *in vivo*. Therefore, the claimed method is only enabled to the intratumoral or intravenous delivery.

In response to the rejection, Applicants further argue that the claimed method is enabled to its full scope wherein any carboxylesterase can be used in said method. Applicants argue that the specification also teach a human intestinal carboxylesterase that may be used in the claimed method. Further, Applicants provide an example of bacterial carboxylesterase in the Declaration that demonstrates carboxylesterase activity *in vitro*. Applicants assert in the Declaration that the carboxylesterase capable of cleaving a prodrug can be identified by assays taught in the specification without undue experimentation. Applicants further demonstrate that a bacterial carboxylesterase identified as being less efficient by the computer model proves to be the same case when tested in enzymatic assay. Applicants therefore conclude that the claimed method is enabled to its full scope wherein any carboxylesterase that cleaves a chemotherapeutic prodrug in said method.

These arguments have been fully considered but deemed unpersuasive. Other than the rabbit carboxylesterase disclosed by the specification, none of the hiCE, bacterial CE and hCE1 demonstrate sufficient activity for conversion of CPT-11 to active drug in an *in vivo* model.

Although there is no undue experimentation in identifying CE that is able to cleave CPT-11 by the computer model, such assay does not predict the successful outcome of the claimed method in an *in vivo* setting for reasons discussed in the previous office actions. As such, the claimed method is enabled to the scope as indicated above.

In response to the rejection, Applicants further argue that the claimed method is enabled to its full scope in which the chemotherapeutic drug can be any prodrug that is cleavable by the carboxylesterase. Applicants assert in the Declaration that such prodrug can be identified by the computer model taught in the specification. Applicants further assert that the Xeloda insert also confirms that drugs other than CPT-11 and APC can be cleaved by a carboxylesterase.

These arguments have been fully considered but deemed unpersuasive. Although there are prodrugs other than CPT-11 and APC can be cleaved by a carboxylesterase, whether a particular carboxylesterase can cleave any prodrug is still unpredictable. Likewise, whether a specific prodrug can be cleaved by any carboxylesterase is also unpredictable. The computer model taught by the Declaration only confirms another type of carboxylesterase can cleave CPT-11 type of prodrug which does not extend to the predictability of successful cleaving any type of chemotherapeutic prodrug *in vivo*. As such, the claimed method is only enabled to the scope discussed above.

Claims 12-14, 18 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants did not indicate whether the above arguments are directed to the enablement rejection or the written description. It appears that the written description rejection was not addressed. Therefore, the claims stand rejected under written description for reasons discussed in detail in the previous office action. Moreover, although carboxylesterase other than rabbit carboxylesterase may be identified by the assay taught in the specification, this alone cannot overcome the written description rejection because the specification has to demonstrate the possession of the invention by either its complete structure or other identifying characteristics. Such structural-functional relationship is not described by the specification for either the term "carboxylesterase capable of cleaving a chemotherapeutic prodrug" or "a chemotherapeutic prodrug capable of being cleaved by a carboxylesterase." As such, this rejection is maintained.

New Grounds of Rejection necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 22, the recitation of "the carboxylesterase is selected from the group consisting of rabbit polynucleotide and human intestinal polynucleotide" renders the claim indefinite because it is unclear how the carboxylesterase can be a rabbit or human intestinal polynucleotide. Carboxylesterase is a protein. Clarification is required.

Regarding claims 23 and 24, the recitation of "the carboxylesterase comprises a rabbit polynucleotide" or "the carboxylesterase comprises a human intestinal polynucleotide" renders the claim indefinite. The specification does not disclose any carboxylesterase that comprises a polynucleotide. It is unclear whether the polynucleotide is attached to the carboxylesterase or simply mixed with the carboxylesterase. As such, the metes and bounds of the claim cannot be established.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.

JAMES KETTER
PRIMARY EXAMINER